



## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA-2022-D-2301]

### Small Volume Parenteral Drug Products and Pharmacy Bulk Packages for Parenteral Nutrition: Aluminum Content and Labeling Recommendations; Draft Guidance for Industry; Availability

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice of availability.

**SUMMARY:** The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled “Small Volume Parenteral Drug Products and Pharmacy Bulk Packages for Parenteral Nutrition: Aluminum Content and Labeling Recommendations.” This draft guidance is intended to clarify the key factors in determining the appropriate aluminum content in a small volume parenteral (SVP) drug product and/or a pharmacy bulk package (PBP) intended as a component of parenteral nutrition (PN) and provide FDA’s recommendations regarding the concentration of aluminum in SVP drug products and PBPs for PN. Additionally, this guidance is intended to assist applicants in determining the appropriate content and placement of information on aluminum in SVP and PBP human prescription drug product labeling.

**DATES:** Submit either electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

**ADDRESSES:** You may submit comments on any guidance at any time as follows:

#### *Electronic Submissions*

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

#### *Written/Paper Submissions*

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

*Instructions:* All submissions received must include the Docket No. FDA-2022-D-2301 for "Small Volume Parenteral Drug Products and Pharmacy Bulk Packages for Parenteral Nutrition: Aluminum Content and Labeling Recommendations." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly

viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- **Confidential Submissions**--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at:  
<https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

*Docket:* For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001

New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

**FOR FURTHER INFORMATION CONTACT:** Thao Vu, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 5232, Silver Spring, MD 20993-0002, 241-308-2929.

**SUPPLEMENTARY INFORMATION:**

I. Background

FDA is announcing the availability of a draft guidance for industry entitled “Small Volume Parenteral Drug Products and Pharmacy Bulk Packages for Parenteral Nutrition: Aluminum Content and Labeling Recommendations.” Aluminum, one of the most abundant metallic elements on earth, occurs naturally in several minerals, ores, oxides, and silicates. Although humans are exposed to aluminum through drinking water, foods, and drugs, aluminum’s oral bioavailability is poor, so healthy individuals typically face little risk of toxicity. Despite that, aluminum toxicity has been documented in medical literature for more than 30 years, with manifestations that include osteomalacia and reduced bone mineralization, neurological dysfunction and dialysis encephalopathy, microcytic hypochromic anemia, and cholestasis.

A long-implicated, major source of aluminum exposure is PN, resulting from contamination of ingredients. Patients with underlying renal impairment who receive prolonged courses of PN support are at greatest risk of exposure to toxic levels of aluminum from PN. Preterm neonates and infants who often require many days of PN support and have immature kidneys that are incapable of excreting aluminum efficiently are at particularly high risk.

Research indicates that patients with renal impairment, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 microgram/kilogram/day

(mcg/kg/day) accumulate aluminum at levels associated with central nervous system and bone toxicity. Because patients with renal impairment, including all preterm neonates, comprise a major portion of those requiring PN support, we recommend that the total aluminum exposure (TAE) from PN uniformly should not exceed 5 mcg/kg/day. To determine TAE, one must consider all sources of aluminum content in PN, including each large volume parenteral and each SVP drug product and PBP in PN. This guidance describes an approach to deriving the recommended aluminum concentration limit in an SVP drug product for PN, based on the proposed clinical dose, concentration of drug or dose volume, and the known or estimated contribution of aluminum from other products in the PN.

Additionally, this guidance is intended to assist applicants in determining the appropriate content and placement of information on aluminum in SVP and PBP human prescription drug product labeling. This guidance provides recommendations to help ensure that information on the aluminum content is appropriate and placed in the proper sections and subsections within the Highlights of Prescribing Information and on the container label and carton labeling. This will help to assure that the information is clear and accessible to healthcare practitioners and includes content that guides the safe and effective use of the drug product.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on "Small Volume Parenteral Drug Products and Pharmacy Bulk Packages for Parenteral Nutrition: Aluminum Content and Labeling Recommendations." It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

## II. Paperwork Reduction Act of 1995

While this guidance contains no collection of information, it does refer to previously approved FDA collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521) is

not required for this guidance. The previously approved collections of information are subject to review by OMB under the PRA. The collections of information in 21 CFR part 314 have been approved under OMB control number 0910-0001. The collections of information in 21 CFR part 312 have been approved under OMB control number 0910-0014. The collections of information in FDA’s guidance entitled “Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products” (available at <https://www.fda.gov/media/109951/download>) have been approved under OMB control numbers 0910-0001 and 0910-0429. The collections of information in 21 CFR 201.56 and 201.57 have been approved under OMB control number 0910-0572. The collections of information in FDA’s guidance entitled “Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA” (available at <https://www.fda.gov/media/107626/download>) have been approved under OMB control number 0910-0718. The collections of information in FDA’s guidance entitled “Controlled Correspondence Related to Generic Drug Development” (available at <https://www.fda.gov/media/109232/download>) have been approved under OMB control number 0910-0797.

### III. Electronic Access

Persons with access to the internet may obtain the draft guidance at <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>, or <https://www.regulations.gov>.

Dated: December 1, 2022.

**Lauren K. Roth,**

*Associate Commissioner for Policy.*